Table 1. Distribution of Child–Pugh A and B patients among responding and non-responding groups.

	Child-Pugh A	Child-Pugh B
RECIST		
Non-responders	64 (92.8%)	12 (92.3%)
Responders	5 (7.2%)	1 (7.7%)
mRECIST		
Non-responders	30 (43.5%)	5 (38.5%)
Responders	39 (56.5%)	8 (61.5%)
EASL		
Non-responders	29 (42.0%)	5 (38.5%)
Responders	40 (58.0%)	8 (61.5%)

there is an association between a single response and the more clinically relevant end point of survival and demonstrated a clear relationship, without the need for a confirmatory scan. Finally the reliability of EASL and mRECIST is questioned because of the influence of lipiodol which makes the distinction between necrosis and vascularity difficult in contrast enhanced scans. In our study, patients did not receive lipiodol and, in a previous meta-analysis, we have shown that there is no clinical data to support its use [2]. Furthermore, the increasing use of drug eluting beads as a more standardised and less toxic method of delivering TACE [3] will allow the application of mRECIST or EASL criteria without the confounding influence of lipiodol.

We acknowledge that ours is a retrospective study which requires prospective validation but were reassured by another recently published retrospective study that confirmed our key findings that EASL and mRECIST are independent predictors of overall survival in patients undergoing transarterial embolisation [4]. A prospective validation is being undertaken in the ongoing TACE 2 trial (ClinicalTrials.gov Identifier NCT01324076).

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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The “pegylated” story continues – Perhaps because both ends (α2a and α2b) are true?

To the Editor:

We want to comment on the article by Prati *et al.* [1] showing decreased response rates to pegylated interferon (PegIFNα) 2b plus ribavirin (RBV) in HCV patients with higher Ishak fibrosis stages (S0–2 *vs.* S3–4 *vs.* S5–6), while response rates to PegIFNα2a + RBV remained similar (or – to be more precise – did not significantly decrease) across patient groups with mild (S0–2), moderate (S3–4), and severe (S5–6) Ishak fibrosis stages. In logistic regression analysis, PegIFNα2b (*vs.* PegIFNα2a) treatment was associated with treatment failure in patients with moderate to advanced fibrosis ⩾S3 (OR 2.83) [1]. The data was derived from a sub-analysis of the prospective MIST study [2], a trial that was designed to compare safety and antiviral efficacy of PegIFNα2a + RBV *vs.* PegIFNα2b + RBV in patients with chronic HCV infection. An important methodological “advantage” of the MIST study (compared to the IDEAL study [3]) is represented by the fact that both patients on PegIFNα2a- and PegIFNα2b-based treatments received exactly the same RBV dosing regimen, while in the IDEAL study RBV was dosed according to the manufacturer’s instructions.

In this re-analysis of the MIST study [2], PegIFNα2a or PegIFNα2b were randomly assigned to patient groups stratified according to HCV genotype but not by fibrosis stage. Even though the prevalence of advanced fibrosis (Ishak score S5 + 6) was similar between patients treated with PegIFNα2a and PegIFNα2b, the lack of stratification according to fibrosis stage may represent a potential bias in baseline characteristics. In addition, only a small subgroup of patients with advanced fibrosis (S5–6) were included in the MIST study (n = 43 in the PegIFNα2a group; n = 39 in the PegIFNα2b group). Last but not least, *IL28B* single nucleotide

Table 1. Comparison of the antiviral efficacy of PegIFNα2a *vs.* PegIFNα2b in combination with ribavirin in HCV patients with METAVIR F4 cirrhosis.

	PegIFNα2a + RBV	PegIFNα2b + RBV	*p* value
Patients, n	69	30	
Cirrhosis METAVIR F4, n (%)	69 (100)	30 (100)	n.a.
Gender [M/F] (%)	53/16 (77)	23/7 (77)	1.000
Age (yr)	49 ± 8	52 ± 10	0.344
Liver stiffness (kPa)	21.1 ± 15.6	24.0 ± 15.3	0.276
HVPG (mmHg)	10.7 ± 5.8	11.1 ± 5.7	0.520
IL28 C/C, n (%)	16 (23)	12 (40)	0.087
IL28 T/C or T/T, n (%)	53 (77)	18 (60)	0.087
HCV-GT 1	45	15	n.a.
HCV-GT 2	0	1	n.a.
HCV-GT 3	11	6	n.a.
HCV-GT 4	13	8	n.a.
HCV GT-1/4, n (%)	58 (84)	23 (77)	0.408
BL HCV-RNA >600,000 IU/ml, n (%)	38 (55)	18 (60)	0.646
Baseline HCV-RNA [log IU/ml]	5.94 ± 0.73	5.83 ± 0.57	0.448
Log drop at wk 2 [log IU/ml]	1.91 ± 1.33	1.38 ± 1.29	0.285
Log drop at wk 4 [log IU/ml]	2.32 ± 1.69	2.13 ± 1.80	0.270
Log drop at wk 8 [log IU/ml]	3.00 ± 2.15	3.62 ± 2.01	0.179
Log drop at wk 12 [log IU/ml]	3.56 ± 2.09	3.96 ± 2.27	0.193
RVR, n/n (%)	9/69 (13)	6/30 (20)	0.374
cEVR, n/n (%)	20/69 (29)	11/30 (37)	0.433
ETR, n/n (%)	30/69 (43)	14/30 (47)	0.714
SVR, n/n (%)	21/69 (30)	12/30 (40)	0.333
SVR GT 1/4, n/n (%)	16/58 (28)	7/23 (30)	0.840
SVR GT 2/3, n/n (%)	5/11 (45)	5/7 (71)	0.278
IL28 C/C			
RVR, n (%)	5/16 (31)	3/12 (25)	0.730
SVR, n (%)	8/16 (50)	4/12 (33)	0.376
GT 1/4 - RVR, n (%)	2/12 (17)	2/9 (22)	0.776
GT 1/4 - SVR, n (%)	5/12 (42)	2/9 (22)	0.349
GT 2/3 - RVR, n (%)	3/4 (75)	1/3 (33)	0.317
GT 2/3 - SVR, n (%)	3/4 (75)	2/3 (67)	0.826
IL28 non-C/C			
RVR, n (%)	4/53 (8)	2/18 (11)	0.699
SVR, n (%)	13/53 (25)	8/18 (44)	0.133
GT 1/4 - RVR, n (%)	3/46 (7)	1/14 (7)	1.000
GT 1/4 - SVR, n (%)	11/46 (24)	5/14 (36)	0.378
GT 2/3 - RVR, n (%)	1/7 (14)	1/4 (25)	0.659
GT 2/3 - SVR, n (%)	2/7 (29)	3/4 (75)	0.175

polymorphisms (SNPs) that have not been assessed in the MIST study [2] – and have not been retrospectively re-tested – can clearly influence response rates and could have introduced a bias in an important baseline variable with direct influence on response rates [1].

When taking a closer look at the data of the PegIFNα2a group, a decrease in SVR rates from 71% in S0–2 to 53% in S5–6 patients was also observed in patients treated with PegIFNα2a + RBV – a difference of 18% in the SVR rate. Even if the SVR rates to PegIFNα2a + RBV treatment are statistically not different between patients with S0–2, S3–4, and S5–6, these differences would certainly be significant if the number of included patients was increased. In addition, an advanced fibrosis stage was identified as independent risk factor of treatment failure for both pegylated interferons in combination with ribavirin for treatment of chronic HCV infection [4,5].

In contrast to SVR rates, RVR rates were similar in patients treated with PegIFNα2b + RBV across fibrosis stages. In this context, it would be important to have more information about dose reductions and early treatment discontinuations in the subgroups with specific fibrosis stages. Overall, more patients allocated to the PegIFNα2b + RBV group had early treatment discontinuation than in the PegIFNα2a + RBV group (n = 73 *vs.* n = 46). This higher rate of treatment discontinuations in PegIFNα2b + RBV patients despite similar rates of (S)AEs may also have biased SVR data when comparing PegIFNα2a to PegIFNα2b patients.

Since the "hyporesponsiveness" to PegIFNα2b + RBV was observed both in moderate (S3/4) and advanced (S5/6) stages of fibrosis [1], further data in other cohorts of cirrhotic patients treated with different forms of PEGIFN (2a *vs.* 2b) are of clinical interest. Since in the era of DAAs a PEGIFN + RBV "backbone" is still needed, differences in response rates between PegIFNα2a and PegIFNα2b used in triple therapies may then influence response rates.

If PegIFNα2b + RBV performs worse than PegIFNα2a + RBV in advanced fibrosis, we would hypothesize that a difference may be even more evident when restricting the comparison to cirrhotic patients with and without portal hypertension as included in our recent study [6]. Thus, we re-analysed data from our previous study in cirrhotic (F4 METAVIR) patients [6]. This was a prospective, non-randomized study including only patients with histologically proven METAVIR F4 cirrhosis [6]. Since no clear evidence of a difference in the efficacy between PegIFNα2b and PegIFNα2a was available, both types of pegIFN were used in combination with RBV for antiviral therapy. A total of 99 patients with METAVIR F4 cirrhosis were treated with PegIFNα2a + RBV (n = 69) or with PegIFNα2b + RBV (n = 30). Baseline characteristics and known predictors or treatment response (Table 1) were similarly distributed between patients receiving PegIFNα2a- and PegIFNα2b-based antiviral combination therapy. The additional information on *IL28B* SNP allowed us to perform subgroup analysis in C/C and non-C/C patients to avoid potential bias derived from potentially heterogeneous baseline characteristics in the PegIFNα2a *vs.* PegIFNα2b groups. In patients with *IL28B* C/C SNP, RVR ($p = 0.730$) and SVR ($p = 0.376$) rates were similar between PegIFNα2a- and PegIFNα2b-based treatment groups.

Among patients with *IL28B* non-C/C SNP, PegIFNα2a + RBV and PegIFNα2b + RBV treatments resulted in similar RVR ($p = 0.699$) and SVR ($p = 0.133$) rates. Even in the most difficult-to-treat patients with *IL28B* non-C/C SNP and HCV-GT1/4 infections, response rates were similar between PegIFNα2a- and PegIFNα2b-treated patients, with SVR rates of 24% for PegIFNα2a + RBV and 36% for PegIFNα2b + RBV.

Our results have to be interpreted by considering all potential problems of a post hoc analysis performed with data of a prospective study that was not designed to demonstrate non-inferiority of PegIFNα2b to PegIFNα2a (or *vice versa*). In addition, the drug-compliance to PegIFNα2a/PegIFNα2b and potential bias arising from problems with self-application of PegIFNα2a syringes and PegIFNα2b pens by cirrhotic patients were not addressed and should be investigated in prospective trials.

In summary, the recently published data of the MIST study by Prati *et al.* [1] provide important information about virologic response rates to PegIFN + RBV combination therapy among patients with specific fibrosis stages. Response rates were reported to be lower in moderate and advanced fibrosis when using PegIFNα2b + RBV therapy but not if PegIFNα2a + RBV is used [2]. In contrast, our analysis including data on HCV genotype and *IL28B* SNPs did not show significant differences in RVR and SVR rates between patients receiving PegIFNα2a + RBV or PegIFNα2b + RBV regimens.

Thus – if all known predictors of treatment response were considered – no significant differences in virologic response rates between the two different types of pegylated interferons have been demonstrated in any analysis so far.

Conflict of interest

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